

## **REMARKS**

The withdrawal of the rejection under 35 U.S.C. §112 and the obviousness-type double patenting rejection is respectfully acknowledged.

### **The First Rejection under 35 U.S.C. §103**

The rejection of claims 1, 3, 4, 9, 10, 15-17, 19-21, 23, 25, 26, 31-37, 39 and 63-66 under 35 U.S.C. § 103, as being obvious over the combination of Nishimura (Allergology) and Banholzer (U.S. Patent No. 5,610,163), is respectfully traversed.

Applicants maintain their position that the combined reference teachings fail to create a prima facie case for obviousness of the claimed invention. Applicants also maintain their position that the previously submitted Declaration under 37 C.F.R. §1.132 provides further clear and convincing evidence of the nonobviousness of the claimed invention.

Applicants take strong issue with the allegation in the Office action that they admitted that Nishimura shows synergism in the combination of oxitropium bromide (an anticholinergic agent) and beclomethasone dipropionate (a corticosteroid). To the contrary, applicants stated directly the opposite. For example, applicants stated in the previous Reply (page 9, lines 8-9): “Further, even for the combination of a different anticholinergic and steroid in Nishimura, there is **no** suggestion of synergistic effect” (emphasis added) and (page 10, lines 1-9):

There are no teachings in the prior art from which one of ordinary skill in the art would have an expectation that the combination of tiotropium and ciclesonide could provide an effect significantly greater than their additive effect. The teachings of Nishimura regarding the oxitropium/beclomethasone combination certainly provide no such expectation. To the contrary, Nishimura itself indicates that the addition of the oxitropium to beclomethasone provided only a “small improvement” in treatment; see the concluding discussion on pg. 87. None of the cited prior art references give any suggestion that a combination of an anticholinergic and a corticosteroid would be expected to result in a synergistic advantageous property.

Applicants fail to see how this could be interpreted as an admission that Nishimura’s combination provides a synergistic effect when applicants’ argument absolutely and directly contrary to such an admission. Applicants urge that this clearly erroneous allegation in the Office action be withdrawn.

As a result, applicants urge that the position taken in the Office action, i.e., that the synergistic effect of the claimed invention demonstrated by applicants is not unexpected, is not supported by the evidence. To the contrary, the Nishimura reference itself makes clear that the combination taught therein does not provide any significant additive or synergistic effect.

It is also alleged in the Office action that applicants must show that the unexpected advantages also provide a significant and practical advantage. As for the significance of the synergistic advantage, this should be self-evident from the data and graphically shown in the graph attached to the declaration. For example, the declaration shows that the bronchoprotective effect of the ciclesonide 0.1 mg/kg was 5% at 3 hours and 5% at 24 hours and the bronchoprotective effect of the tiotropium bromide 0.06 mg/kg was 35% at 3 hours and 12% at 24 hours. Their combination, however, according to the invention, provided bronchoprotection of 49% at 3 hours and maintain 41% bronchoprotection after 24 hours. Thus, the sustained bronchoprotection effect for the claimed combination was more than twice that of the added effect of the two components separately. As for the practicality of the effect, it should be self-evident that the observed surprising bronchoprotective effect is highly practical for using the combination in treating respiratory diseases. The specification as a whole supports that the bronchoprotective activity makes the compounds useful for treating such diseases.

For the above reasons, applicants submit that the counter-arguments provided in the Office action are not supported on the record. Thus, applicants stand by their previous points in support of nonobviousness and re-emphasize them, as follows.

The data provided in the Declaration provides a clear and convincing showing of significant unexpected advantages for applicants' particular combination. The data show that the combination of tiotropium and ciclesonide provides a surprising and synergistic advantageous benefit in bronchoprotective activity. Treatment with the combination of these specific actives gave a bronchoprotective effect significantly more than the sum of the activities achieved with each separately. Ciclesonide applied at 0.1 mg/kg only induced slight bronchoprotection of about  $5\% \pm 10\%$ , 3 hours after drug inhalation which remained constant over 24 hours. Tiotropium bromide displayed a dose-dependent bronchoprotection which reached  $35\% \pm 25\%$  at 0.06  $\mu\text{g/kg}$ , 3 hours after inhalation. The compound retained at

the end of the study a bronchoprotection of  $12\% \pm 7\%$ . The combination of ciclesonide (0.1 mg/kg) and tiotropium bromide (0.06 µg/kg) resulted in an unexpected super-additive bronchoprotection of  $49\% \pm 7\%$  at 3 hours and of  $41\% \pm 14\%$  after 24 hours. The combined administration of tiotropium bromide and ciclesonide resulted in a clearly synergistic bronchoprotection in this model. In particular the effect of the combination was significantly higher than the sum of the values of the respective mono-therapies. Such synergistic effect could not have been expected from the cited prior art. Certainly, the references fail to provide any suggestion of the advantage of applicants' particular combination since neither of the references provide any suggestion to use ciclesonide, particularly, together with a tiotropium compound. Further, even for the combination of a different anticholinergic and steroid in Nishimura, there is no suggestion of synergistic effect. The data of unexpected, synergistic advantages, thus, provides further support for the nonobviousness of the claimed invention. If the references established a prima facie case of obviousness, this proof of nonobviousness would overcome the prima facie case. Thus, it provides an independent basis for withdrawal of the rejection.

It was further alleged in the previous Office action that applicants did not provide a comparison of the claimed composition with any combination of a corticosteroid and an anticholinergic agent. In response, applicants urge that there is more than one way that nonobviousness can be demonstrated by data and that evidence submitted as a showing of nonobviousness must be considered. The PTO's own manual, at MPEP §716.02(a)(I), makes clear that a showing of synergism can be sufficient proof of nonobviousness, stating:

Evidence of a greater than expected result may also be shown by demonstrating an effect which is greater than the sum of each of the effects taken separately (i.e., demonstrating "synergism"). *Merck & Co. Inc. v. Biocraft Laboratories Inc.*, 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989).

It is not necessary for applicants to provide a comparison to the oxitropium/beclamethasone combination shown by Nishimura because their showing of the synergistic effect of their combination already provides a clear and convincing showing of unexpected properties of the claimed invention. There are no teachings in the prior art from which one of ordinary skill in the art would have an expectation that the combination of tiotropium and ciclesonide could provide an effect significantly greater than their additive effect. The teachings of Nishimura

regarding the oxitropium/beclomethasone combination certainly provide no such expectation.

To the contrary, Nishimura itself indicates that the addition of the oxitropium to beclomethasone provided only a “small improvement” in treatment; see the concluding discussion on pg. 87. None of the cited prior art references give any suggestion that a combination of an anticholinergic and a corticosteroid would be expected to result in a synergistic advantageous property.

Considering the record as a whole, applicants urge that they have provided clear and convincing evidence of significant unexpected advantages of their particular combination. The prior art gives no hint to one of ordinary skill in the art that the specific combination of the specific anticholinergic, tiotropium salt, and the specific corticosteroid, ciclesonide, would be particularly advantageous. Thus, a clear and convincing showing of nonobviousness is provided.

Further, applicants submit that the references fail to establish a prima facie case of obviousness or, at most, only a weak case which is readily overcome by the Declaration, for the following reasons.

Nishimura discloses the use of a combination of oxitropium bromide with a certain inhaled corticosteroid, i.e., beclomethasone dipropionate, for use in treating chronic asthma. Nishimura alleged that the combination of the oxitropium bromide provided advantages over beclomethasone dipropionate alone. But the advantages are only minor and there is no allegation or proof that the advantages are more than merely the additive effect.

Banholzer discloses a generic formula (I) encompassing a range of compounds which includes tiotropium salts. Claim 5 is directed particularly to tiotropium salts.

The basis for the rejection is that it would have been obvious to one of ordinary skill in the art to exchange the oxitropium bromide of Nishimura with the tiotropium compound disclosed in Banholzer. However, such a combination would not meet or suggest the elements of the claims and, thus, not support a prima facie case of obviousness.

The instant claims recite a combination of the tiotropium compound and the particular steroid, ciclesonide. Neither of the references provide any suggestion to combine the particular steroid ciclesonide. Nishimura discloses only a beclomethasone salt and Banholzer provides no teachings regarding any steroid. The combined reference teachings thus fail to meet this claim element.

The instant claims further recite, in addition to the tiotropium compound and the ciclesonide compound, “a pharmaceutically acceptable excipient selected from the group consisting of glucose, arabinose, lactose, saccharose, and maltose.” Neither of Nishimura or Banholzer provide any teaching regarding a composition containing such a particular excipient. Further, the Office action provides no reasoning as to why a composition including this element would be obvious to one of ordinary skill in the art. For this additional reason, therefore, the combined references fail to meet the claim recitations.

For all of the above reasons, it is urged that the cited prior art, considered as a whole on the record, fails to render the claimed invention obvious to one of ordinary skill in the art. Thus, the rejection under 35 U.S.C. § 103 should be withdrawn.

### **The Second Rejection under 35 U.S.C. § 103**

The rejection of claims 1, 3, 4, 9, 10, 15-17, 19-21, 23, 25, 26, 31-37, 39 and 63-66 under 35 U.S.C. § 103, as being obvious over Keller (WO 00/28979, corresp. to U.S. Patent No. 6,645,466), Nishimura (Allergology) and Banholzer (U.S. Patent No. 5,610,163) in combination, is respectfully traversed.

The traversal of the rejection based on Nishimura and Banholzer from above is incorporated by reference here. The primary failing of the combination of Nishimura and Banholzer is the failure to suggest the specific combination of specific components: 1) the tiotropium compound, 2) the ciclesonide compound, and 3) the glucose, arabinose, lactose, saccharose or maltose excipient. Additionally, the combination of Nishimura and Banholzer fails to provide any hint to the unexpected synergistically advantageous properties of the combination specifically of the tiotropium and ciclesonide components.

Keller fails to provide any teachings which make up for the deficiencies of the Nishimura and Banholzer references. Keller discloses adding magnesium stearate to powder formulations to improve their moisture resistance; see, e.g., col. 4, lines 16-25. Keller teaches that its invention can be applied to powders containing a wide variety of active agents and includes tiotropium and ciclesonide as examples of possible actives; see, e.g., col. 6, line 13, to col. 7, line 10. Keller also provides a general discussion of possible excipients which include some of the ones listed in the current claims; see, e.g., col. 8, lines 1-16. However, Keller provides no suggestion to specifically combine tiotropium, ciclesonide and one of the

specific excipients recited in the current claims. Further, Keller certainly provides no hint that such a combination would provide unexpected synergistically advantageous properties, as shown by applicants.

Accordingly, the combination of Keller, Nishimura and Banholzer is equally insufficient in supporting the nonobviousness of the claimed invention as the combination of Nishimura and Banholzer is. This rejection under 35 U.S.C. §103 should, thus, also be withdrawn.

It is submitted that the claims are in condition for allowance. However, the Examiner is kindly invited to contact the undersigned to discuss any unresolved matters.

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,

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Attorney Docket No.: 01-1174-1-C1

Date: February 12, 2009

JAS/dp